The relative renal safety of iodixanol compared with low-osmolar contrast media: a meta-analysis of randomized controlled trials

Reed M, Meier P, Tamhane UU, Welch KB, Moscucci M, Gurm HS

CRD summary
The iso-osmolar contrast medium iodixanol was not associated with lower nephrotoxicity than low-osmolar contrast media overall. However, iodixanol caused significantly less nephrotoxicity than ioxaglate and iohexol. There is no difference in risk when compared with iopamidol, iopromide and ioversol. In view of uncertainties about the quality of the included studies, the reliability of the authors’ conclusions is unclear.

Authors’ objectives
To compare the nephrotoxicity of the iso-osmolar contrast medium iodixanol with low-osmolar contrast media.

Searching
MEDLINE, EMBASE, Web of Knowledge, Cochrane Central Register of Controlled Trials (CENTRAL), Current Contents and IPA databases and Google Scholar were searched for the period 1980 to November 2008. Search terms were reported. Abstracts from the 2006 to 2008 meetings of American Heart Association, American College of Cardiology, European Society of Cardiology and Transcatheter Cardiovascular Therapeutics were searched for the period 2006 to 2008. Other internet-based sources of information were screened.

Study selection
Randomised controlled trials (RCTs) that compared iodixanol to low-osmolar contrast media (LOCM) in patients who underwent contrast media application were included. Included trials needed to provide data on renal function for all patients. The primary outcome was incidence of contrast-induced acute kidney injury (as defined in the primary studies). Secondary outcomes were need for renal replacement therapy and mortality. Outcomes were measured after one to seven days.

The most commonly used definitions of contrast-induced acute kidney injury were serum creatinine elevation of greater than 25% or greater than 50%, serum creatinine greater than 0.5mg/dL or glomerular filtration rate reduced by greater than 25%. Both intravenous and intra-arterial contrast were used. Mean contrast volume ranged from 104.1 to less than 1,000mL. Most trials used prophylactic hydration; some trials used prophylactic N-acetylcysteine. LOCM used in the included studies were mostly non-ionic monomers (iopromide, iopamidol, ioversol, iomeprol and iohexol); there was one ionic dimer (ioxaglate). Many trials were of patients with moderate or severe renal insufficiency. Reasons for undergoing contrast included coronary and/or peripheral angiography or intravenous computed tomography. Patients’ mean age ranged from 54.5 to 71.9 years. The proportion of males ranged from 42% to 88%. The proportion of patients with diabetes ranged from 21% to 100%. Baseline serum creatinine ranged from 1.04mg/dL to 1.96mg/dL.

The authors did not state how many reviewers performed the selection of relevant studies.

Assessment of study quality
Trial quality was assessed by evaluation of study design and included concealment of allocation, blinding and intention-to-treat analysis.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
The number of events for each outcome was extracted in order to calculate risk ratios (RR) and 95% confidence intervals (CI). Three independent reviewers extracted data. Disagreements resolved by consensus. Study investigators were contacted for further information when necessary. Attempts were made to retrieve data from the original source in unpublished studies.
Methods of synthesis

Pooled risk ratios (RRs) with 95% CIs were calculated using a random-effects model and intention-to-treat analysis. A continuity correction was used when an event did not occur in one group. Between-study heterogeneity was determined using $I^2$ and Q-statistic tests. The effect of individual studies on the summary estimate was determined by omitting one study at a time from the pooled analysis. Publication bias was assessed by formal testing using rank order correlation, Egger's test, Orwin fail-safe $N$ and based on a visual assessment of a funnel plot. Meta-regression using a mixed-effect model was used to assess the impact of selected variables on incidence of contrast-induced acute kidney injury.

Results of the review

Sixteen relevant RCTs were identified ($n=2,763$, range 72 to 414).

The pooled analysis found no significant difference in overall risk of contrast-induced acute kidney injury between iodixanol and LOCM (RR 0.79, 95% CI 0.56 to 1.12; 14 RCTs). There was low to moderate heterogeneity ($I^2=45\%$).

No significant differences in risk were found in subgroup analyses for patients with coronary angiography, diabetes patients and when individual studies were eliminated from the analysis. Meta-regression showed that none of the selected variables impacted on incidence of contrast-induced acute kidney injury.

Pooled analyses stratified by specific LOCMs showed a significantly lower risk of contrast-induced acute kidney injury with iodixanol compared to iohexol (RR 0.19, 95% CI 0.07 to 0.56; two RCTs) and ioxaglate (RR 0.58, 95% CI 0.37 to 0.92; three RCTs). There were no significant differences in risk for iodixanol compared to iopamidol (three RCTs), iopromide (four RCTs) and ioversol (one RCT). There was no evidence for publication bias.

There was no statistically significant difference between iodixanol and LOCM in need for haemodialysis (12 RCTs) or deaths (nine RCTs) when studies were pooled (few events were reported for either outcome).

Authors’ conclusions

This meta-analysis included 2,763 participants and suggested that iodixanol when compared with LOCM overall was not associated with less contrast-induced acute kidney injury. The relative renal safety of LOCM compared with iodixanol may vary based on the specific type of LOCM.

CRD commentary

The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched. It was unclear whether language restrictions were applied and whether unpublished studies were included. Publication bias was assessed. Study quality was assessed, but not reported. Data extraction was carried out with efforts to reduce error and bias; it was not reported whether this process applied to other aspects of the review process. Relevant study details were reported, but there were no details of loss to follow-up. Statistical heterogeneity was assessed. The statistical method used for meta-analysis of the RCTs was appropriate and an intention-to-treat analysis was performed. Relevant subgroup analyses were performed. In view of uncertainties about the quality of the included studies, the extent to which the authors’ conclusions are reliable is unclear.

One author participated in an education programme sponsored by a contrast media manufacturer.

Implications of the review for practice and research

**Practice:** The authors stated that due to the results of this review, revision of the 2007 ACC/AHA guidelines update recommending use of iso-osmolar contrast media for coronary angiography in the setting of unstable angina or non-ST-segment elevation myocardial infarction and renal insufficiency may be necessary.

**Research:** The authors recommended further trials to compare various iso-osmolar and low-osmolar media and determine the optimal contrast agent for use in patients with chronic renal insufficiency and investigate the impact on long-term outcomes.
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